Comparison of Folicular, Hurthle Cell Neoplasm and Oncocytic Changes Diagnosed by Thyroid Fine Needle Aspiration with Postoperative Histopathological Results

Tiroid İnce İğne Aspirasyon Biyopsisinde Foliküler, Hurthle Hücreli Neoplasm ve Onkositik Değişikliklerin Postoperatif Histopatolojik Sonuçları ile Karşılaştırılması

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Abstract

Purpose: Main diagnostic method of thyroid nodules is fine needle aspiration biopsy (FNAB), but sensitivity of this method in the evaluation of follicular lesions is low. We reevaluated patients who underwent operation with FNAB reports of follicular neoplasm, Hurthle cell neoplasm and oncocytic changes. Postoperative histopathological examination and thyroid ultrasound (TUS) results, scintigraphic features of nodules were reevaluated.

Material and Method: One hundred and three patients who were diagnosed with FNAB as follicular neoplasm, Hurthle cell neoplasm, oncocytic changes and who underwent thyroidectomy were reevaluated, retrospectively. FNAB and postoperative histopathological thyroidectomy specimen results were compared.

Results: Comparison results of FNAB cytologic evaluation and postoperative histopathological examination of those nodules were as follows. Eight patients who were diagnosed as follicular lesion in FNAB were papillary carcinoma, 6 were follicular carcinoma. One patients who were diagnosed as Hurthle cell neoplasm in FNAB was papillary carcinoma. Six patients who were diagnosed as oncocytic changes in FNAB were papillary carcinoma. According to postoperative histopathology results, all patients' diagnoses were as follows: 21 patients (20.4%) were diagnosed with thyroid malignancy in which 15 patients (14.6%) were papillary carcinoma, 6 patients (5.8%) were follicular carcinoma. Hypoechoic appearance of nodule in TUS was found to be the only independent risk factor in prediction of malignancy.

Discussion: One fifth of the patients who were reported as follicular neoplasm, Hurthle cell neoplasm and oncocytic changes in FNAB were consistent with malignancy. Hypoechoic appearance of these nodules in TUS was found to be an independent risk factor in prediction of malignancy. *Turk Jem 2014; 1: 5-12*

Key words: Thyroid cancer, follicular; Thyroid cancer, Hurthle cell; Biopsy, Fine-Needle

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Özet

Amaç: Günümüzde tiroid nodüllerinde temel tanısal yöntem tiroid ince iğne aspirasyon biopsisi (TİİAB) olmasına rağmen foliküler lezyonların değerlendirilmesinde duyarlılığı düşüktür. Çalışmamızda TİİAB sonucu foliküler neoplazm, onkositik değişiklik ve Hurthle hücreli neoplazm olarak raporlanan ve opere edilen hastaların, postoperatif histopatolojik inceleme sonuçlarını, nodüllerin sintigrafik özelliklerini, tiroid ultrasonografi (TUS) bulgularını değerlendirdik.

Gereç ve Yöntem: Çalışmamızda tanısal amaçlı TİİAB yapılan hastalar incelenmiş olup, TİİAB sonucu foliküler neoplazm, onkositik değişiklik ve Hurthle hücreli neoplazm olarak raporlanan ve tiroidektomi yapılan 103 hasta retrospektif olarak değerlendirildi. TİİAB sonucu ve tiroidektomi materyalinin TİİAB yapılan nodüllerin postoperatif histopatolojik inceleme sonuçları karşılaştırıldı.

Bulgular: TİİAB sitolojik değerlendirme ve postoperatif histopatolojik inceleme sonuçları karşılaştırıldığında: foliküler neoplazm olarak değerlendirilen hastaların 8'i papiller karsinom, 6'sı foliküler karsinom; hurthle hücreli neoplazm olarak değerlendirilen sitolojilerin 1'i papiller karsinom; onkositik değişiklik olarak değerlendirilen hastaların ise 6'sı papiller karsinom olarak yorumlandı. Tüm olgular için postoperatif histopatoloji sonuçları değerlendirildiğinde olguların %20,4'nün tiroid malignitesi olduğu, bunların 15'nin (%14,6) papiller karsinom, 6'sının (%5,8) foliküler karsinom olduğu görüldü. TUS'de nodülün hipoekoik izlenmesi malignite için tek bağımsız öngördürücü faktör olarak tespit edildi.

Tartışma: TİİAB sonucu foliküler neoplazm, onkositik değişiklik ve hurthle hücreli neoplazm olarak raporlanan olgularında bu nodüllerin histopatolojik sonuçlarının, 1/5'inde malignite olduğu ve TUS'de bu nodüllerin hipoekoik görünümü maligniteyi öngördürmede bağımsız bir risk faktörü olduğu izlenmiştir. Turk Jem 2014; 1: 5-12

Anahtar kelimeler: Tiroid kanser, foliküler, hurthle hücreli karsinom, biopsi, ince iğne aspirasyon biopsisi

Çıkar çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Introduction

Nodular thyroid disease is a common disorder of the endocrine system characterized by one or more nodules in the thyroid gland (1). The most common cause is iodine deficiency (2). The incidence of thyroid nodules in the general population is 3%-5% with palpation, 40%-50% by autopsy and 30%-40% by ultrasound (US) respectively (2,3,4). Thyroids' nodular disease can be neoplastic or non-neoplastic. Independent from the size of the thyroid nodule prevalence of cancer has been found to be 5%-10%, on top of that on autopsy data, the ratio is as high as 6-35% (5,6). Early diagnosis of thyroid cancer is very important due to the indolent nature of the disease and long life expectancy after early treatment.

Today, the basic diagnostic method of thyroid nodule is fine needle aspiration biopsy of the thyroid (FNAB). Being safe with low-cost and accurate results, this method is the first choice in the diagnosis of thyroid nodules. US guidance and the presence of a cytopathologists increases the rate of correct diagnosis (7,8,9) FNAB reveals the character of many nodular thyroid lesions and it is helpful in determining patients who should undergo surgical treatment. However, the sensitivity is low in the evaluation of follicular lesions (9,10,11). Thyroid follicular cell mediated cancers are; papillary thyroid carcinoma, follicular thyroid cancer and Hurthle cell (oncocytic) thyroid cancer. Only 15 to 25% of the FNAB results reported as follicular neoplasm are malignant (12,13,14). Thus, 80% of the cases who were reported as follicular neoplasm and its variants (hurthle cell and oncocytic) are benign lesions according to their histological examination and these patients are undergoing unnecessary surgery (14). In our study, we evaluated patients' thyroid US findings, age, gender, goiter type, cancer, smoking, history of radiation to neck area, scintigraphic features and post-operative histopathological examination whose FNAB results were reported as follicular neoplasm, oncocytic change and hurthle cell neoplasm and had thyroid surgery.

Materials and Methods

In this study, we enrolled patients retrospectively whose FNAB results were reported as follicular neoplasms, oncocytic change or Hurthle cell neoplasm, and had surgery after FNAB. These patients were evaluated between 2009-2012 in Düzce University, Medical Faculty Hospital Endocrinology outpatient clinic. Local ethical comitte aproval was taken

In all patients who got diagnosed with growth or nodule in the thyroid gland by physical examination in outpatient clinics, thyroid US verification and thyroid function tests (thyroid-stimulating hormone "TSH" and free T4) was performed. Thyroid US was performed in the endocrinology department by the same endocrinologist by using 4-10 MHz superficial linear probe (GE LOGIQ 3 10L). During US, the right and left thyroid lobe and isthmus size, nodular structure, echogenicity (hypoechoic, isoechoic, hyperechoic, cystic, mixed), nodule long size-short size (LS / SS), calcification and calcification type (microcalcifications, wall calcification, coarse calcifications) were recorded.

Thyroid scintigraphy was performed in patients who had suppressed TSH. Scintigraphic features of the nodules were recorded as hypoactive (cold), isoactive or overactive (hot). US-guided FNAB was performed on all of the nodules by the same person. Written consent was taken from all patients prior to FNAB and surgery.

US guided FNAB procedure was performed with 10 ml syringe with a 21 gauge needle after cleansing of the skin with patients head slightly extended to back. During the process we did not need to use anesthetic agents. During the aspiration, needle was moved into various positions within the nodule and we vacuumed the nodule while moving the needle back and forth. The material taken from the nodule was spreaded to the slide and it was allowed to air dry and was sent to pathology unit for cytological evaluation purposes. After staining, the preparations were evaluated by the same pathologist. Cytology results were classified as without atypia, malignant, suspicious for malignancy, papillary carcinoma, follicular neoplasm, Hurthle cell neoplasm, oncocytic change and inadequate cytology. In the cases considered as inadequate cytology procedure was repeated. If FNAB cytology results were detected as follicular neoplasm, Hurthle cell neoplasms or oncocytic change; these patients were consulted to the general surgery unit for thyroidectomy. Postoperative histopathological results were compared with the long dimension of nodules, nodules' long dimension and a short dimension ratio and with the age range. Age groups were classified as under 45, 46-60 age group, 61-75 age group and older than 75 years old group. Nodule size was categorized as above 15mm or equal-under 15mm. Long size-short size ratio were classified as ≤ 1.5, 1.5-2.5 and above 2.5. 123 patients were operated but we could not reach to the postoperative results of 20 of these patients. After the operation, thyroidectomy material was evaluated by the same pathologist. Pathological findings were defined as benign papillary carcinoma, follicular cancer, medullary cancer and anaplastic cancer. FNAB cytology results reported as without atypia, malignant or suspicious for malignancy were excluded from the study.

Statistical Analysis

Statistical analyzes were performed with the SPSS computer software (ver. 18.0 for Windows, SPSS Inc, Chicago, IL, USA). Nominal data were compared with Pearson's chi-square test or Fisher's Exact chi-square test using 2x2 tables between independent groups and the results was expressed as frequency and percentage (%). Bonferroni correction was used when multiple comparisons were made and $p<0.05 / 3=0.017$ was considered as significant limit. Numeric data showing normal distribution was compared in two groups. When comparing independent samples t test was used and the mean ± standard deviation were used as descriptive values. Numerical data which do not show normal distribution was compared in more than two groups with the Kruskal-Wallis analysis and median (minimum-maximum) values were used as descriptive values. While investigating independent predictive factors for malignancy, binary logistic regression analysis was used. Forward Variable Screening Method was used as a method. Goodness of fit was assessed by Hosmer-Lemeshow Test. For the evaluation of coefficients of the model, Omnibus Test was used and significance of the model was evaluated. Statistically, p-values less than 0.05 was considered as significant.

Results

Among patients who had their FNAB cytology results reported as follicular neoplasm, oncocytic change or Hurthle cell neoplasm and had surgery, 103 patients were eligible for the study. (81 women and 22 men between the ages of 26-78). 20 patients with unattainable postoperative results were not included in the study. The mean age of the 103 patients enrolled in the study were 48.6±11.1; 47.5±11.1 for women, men 52.9±10.3, respectively (p=0.67). None of the patients included in the study had radiation therapy or history of cancer. 16.5% of the patients had a history of cigarette smoking. 33 (32%) patients had solitary nodular goiter and 70 (68%) patients were diagnosed as multinodular goiter after thyroid US examination. In the FNAB cytologic evaluation results were interpreted as, 68.9% (n=71) follicular neoplasm (56 female, 15 male), 9.7% (n=10) hurthle cell neoplasms (6 women and 4 men) and 21.4% (n=22) oncocytic change (19 female, 3 male). There was no significant correlation between FNAB cytologic evaluation and gender, smoking history or nodule type (Table 1).

We did not detect a statistically significant difference between FNAB cytology results, nodule echogenicity or features of nodular calcification. And there was no statistically significant difference between FNAB cytologic evaluation and the scintigraphic features of nodules (Table 2). In addition, in the statistical analysis, there were no significant differences between FNAB results and the median values of long size of the nodules (follicular: 21 (9-50); hurthle: 22 (10-34); oncocytic: 23 (10-75), p=0.908), nodules' long size-short size ratio (follicular: 1.5 (1-3.3); hurthle: 1.1 (1.08-2.1); oncocytic: 1.4 (1.1-2.5), p=0.171), and patient age (follicular: 48 (26-78); hurthle: 53 (35-62), oncocytic: 48 (29-73), p=0.670).

When we compare FNAB cytological results and post-operative histopathological results: among the group of patient whose results were interpreted as follicular neoplasm, 8 patients had (11.3%) papillary carcinomas, 6 patients had (8.5%) follicular carcinoma and 57 (80.3%) had benign histopathology. Among the group of patient whose results were interpreted as Hurthle cell neoplasms; 1 patient (10%) had papillary carcinoma, 9 patients (90%) had benign histopathology. And among patients with oncocytic change result; 6 patients had (27.3%) papillary carcinomas and 16 patients' (82.7%) results were interpreted as benign histopathology. All patients were evaluated for the post-operative histopathology results, 15 patients (14.6%) had papillary carcinomas, 6 patients (5.8%) had follicular carcinoma and 82 patients (79.6%) had benign histopathology (Figure 1). There was no significant difference between FNAB and postoperative histopathology results for malignancy (p=0.193).

There was no history of neck radiation or cancer in patients who got diagnosed with carcinoma. There were no significant differences between postoperative histopathology results (papillary carcinoma, follicular carcinoma and benign histopathology) and gender, type of goiter, thyroid history or smoking history. We compared postoperative histopathology results and FNAB cytology with US features (echogenicity, long size, calcification) of nodules which were reported as follicular, hurthle cell neoplasms or oncocytic change. Mostly, malignant nodules was found to be hypoechoic on ultrasonography. In terms of calcification no significant difference was found (Table 3).

There were no differences between scintigraphy features and postoperative histopathology results (Table 3). Rate of malignancy in hypoactive nodules was calculated as 21.9%.

We classified FNAB results as (follicular neoplasm-Hurthle / oncocytic cell neoplasms) and when comparison is made again between these two groups in terms of general characteristics of the patients and post-operative malignancy, no difference was found (Table 4).
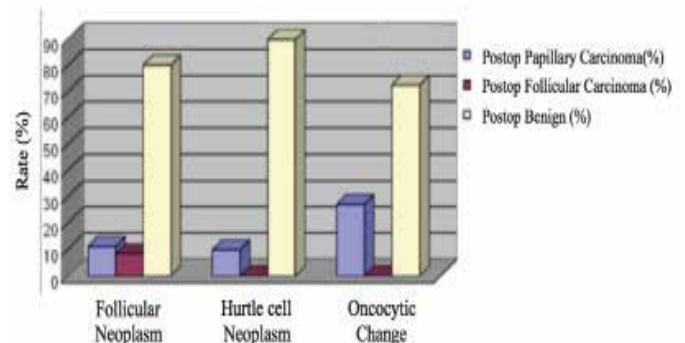
Figure 1. Post-operative histopathological results of the patients who had surgery after FNAB results

Table 1. Patients' characteristics and results from the Fine-Needle Aspiration Biopsy (FNAB) of the Thyroid					
		Follicular Neoplasms n=71 (68.9%)	**Hurthle cell neoplasm n=10 (9.7%)**	**Oncocytic change n=22 (21.4%)**	**P***
Gender	Female	56 (78.9%)	6 (60%)	19 (86.4%)	p₁=0.233 p₂=0.548 p₃=0.165
	Male	15 (21.1%)	4 (40%)	3 (13.6%)	
Type of goiter	Solitary Nodule	22 (31%)	2 (20%)	9 (40.9%)	0.473
	MNG	49 (69%)	8 (80%)	13 (59.1%)	
Smoking history		12 (16.9%)	2 (20%)	3 (13.6%)	p₁=0.681 p₂=1.000 p₃=0.637
* P₁= Follicular and Hurthle; P₂= Follicular and Oncocytic; P₃=Hurthle and Oncocytic					

There was no significant difference between postoperative histopathology results with age (papillary: 46 (26-78); follicular: 43 (37-65); benign: 50 (29-74), p=0.806), nodular long size (papillary: 18 (11-42); follicular: 30 (15-38); benign: 21 (9-75), p=0.186), and nodule long size / short size (LS / SS) median ratio (papillary: 1.4 (1.1-2); follicular: 1:25 (1:08 to 1:55); benign: 1.4 (1-3.3), p=0.404).

We did logistic regression analysis (Hosmer Lemeshow fit test: p=1.000 and model: p=0.005) to find the factors to predict malignancy in nodules whose results were reported as follicular, Hurthle cell neoplasm or oncocytic changes after FNAB. It was found that Ultrasound echo findings were an independent predictor for malignancy (p=0.017).

With reference to eco mixed hypoechoic nodules odds ratio 6.064 were found to be (95% Confidence Interval: 1878-19584, p=0.003). Age, gender, calcification, nodule size and scintigraphic features were not identified as independent predictors.

Eighty-nine patients had total thyroidectomy, one case had subtotal thyroidectomy, 11 patients underwent lobectomy and near-total thyroidectomy was performed in 2 cases. Among the cases of malignancy, 19 patients had total thyroidectomy, one case had subtotal thyroidectomy and one case had

Table 2. The comparison of the results from FNAB to the results of imaging methods

				FNAB Results			
				Follicular Neoplasms (n=71)	Hurthle cell Neoplasms (n=10)	Oncocytic Neoplasms (n=22)	P
Ultrasonography	Echogenicity	(n,%)	Hypoechoic	16 (22.5)	2 (20)	6 (27.3)	p_1=1.000 p_2=0.648 p_3=1.000
			Hyperechoic	5 (7)	0	0	p_1=1.000 p_2=0.335 p_3=…
			Isoechoic	18 (25.4)	3 (30)	4 (18.2)	p_1=0.714 p_2=0.489 p_3=0.648
			Mixed	32 (45.1)	5 (50)	12 (54.5)	p_1=1.000 p_2=0.437 p_3=1.000
	Calcification	(n,%)	None	54 (76.1)	7 (70)	14 (63.6)	p_1=0.702 p_2=0.251 p_3=1.000
			Coarse	8 (11.6)	3 (30)	2 (9.1)	p_1=0.588 p_2=0.072 p_3=0.142
			Peripheral	2 (2.8)	0	0	p_1=1.000 p_2=1.000 p_3= ….
			Micro	7 (9.9)	0	6 (27.3)	p_1=0.132 p_2=1.000 p_3=0.293
Scintigraphy		(n,%)	None	28 (39.4)	5 (50)	9 (40.9)	p_1=0.733 p_2=0.902 p_3=0.712
			Hypoactive	29 (40.8)	3 (30)	9 (40.9)	p_1=0.732 p_2=0.996 p_3=0.703
			Isoactive	4 (5.6)	1 (10)	0	p_1=0.492 p_2=0.569 p_3=0.312
			Hyperactive	10 (14.1)	1 (10)	4 (18.2)	p_1=1.000 p_2=0.734 p_3=1.000

* p_1= Follicular and Hurthle; p_2= Follicular and Oncocytic; p_3=Hurthle and Oncocytic

lobectomy. In post-operative histopathological examination, none of the patients with malignancy had adjacent tissue metastasis, lymph node metastasis or distant metastasis. In cases diagnosed with malignancy, post-operative histopathological examination results were as following; 8 cases had microcarcinoma (6 papillary carcinoma, 2 follicular carcinoma) and 13 cases had macrocarsinoma (9 papillary carcinoma, 4 follicular carcinoma).

Cancer type (micro/macro carcinoma) compared with postoperative pathology showed no statistically significant difference (p>0.05).

Discussion

In patients enrolled in this study whose FNAB results were reported as follicular lesion, oncocytic change or hurthle cell lesion, 20.4%

Tablo 3. The comparison of postoperative histopathology results to the results from imaging methods						
				Postoperative Histopathology		
				Papillary Carcinoma (n=15)	Follicular Carcinoma (n=6)	Benign (n=82)	p
Ultrasonography	Echogenicity	(n,%)	Hypoechoic	8 (53.3)	3 (50)	13 (15.9)	P_1=1.000 P_2=0.003 P_3=0.071
			Hyperechoic	0 (0)	0 (0)	5(6.1)	P_1= … P_2=1.000 P_3=1.000
			Isoechoic	3 (20)	1 (16.7)	21(25.6)	P_1=1.000 P_2=0.756 P_3=1.000
			Mixed	4 (26.7)	2 (33.3)	43(52.4)	P_1=1.000 P_2=0.066 P_3=0.429
	Long size of the nodule	(n,%)	>15 mm	10(12.3)	5(6.2)	66 (81.5)	P_1=0.623 P_2=0.305 P_3=1.000
	Calcification	(n,%)	None	11(73.3)	5(83.3)	59(72)	P_1=1.000 P_2=1.000 P_3=1.000
			Rough	1(6.7)	0(0)	10(12.2)	P_1=0.526 P_2=0.418 P_3=1.000
			Periphery	0(0)	1(16.7)	1(1.2)	P_1=0.286 P_2=1.000 P_3=0.132
			Micro	3(20)	0(0)	12(14.6)	P_1=1.000 P_2=0.685 P_3=0.591
Scintigraphy		(n,%)	None	7(46.7)	2(33.3)	33(40.2)	P_1=0.659 P_2=0.642 P_3=1.000
			Hypoactive	7(46.7)	2(33.3)	32(39)	P_1=0.659 P_2=0.579 P_3=1.000
			Isoactive	0(0)	1(16.7)	4(4.9)	P_1=0.286 P_2=1.000 P_3=0.304
			Hyperactive	1(6.7)	1(16.7)	13(15.9)	P_1=0.500 P_2=0.689 P_3=1.000
p_1=Papillary and Follicular; p_2=Papillary and Benign; p_3= Follicular and Benign						

of them were diagnosed with thyroid cancer according to post-operative examinations. 14.6% of these patients had papillary carcinoma and 5.8% had follicular carcinoma. When we evaluate malignancy predictors in terms of the regression analysis; In patients whose FNAB results were reported as follicular lesion, oncocytic change or hurthle cell lesion, nodules which appeared hypoechoic in ultrasonography were identified as independent predictor factor. In the differentiation of malignant and benign thyroid nodules, there is no precise criteria determined by scintigraphy or ultrasonography. But for more accurate and reliable results in the light of the criterias set for ultrasound and scintigraphy, the most important and widely used method in differentiating benign from malignant is FNAB (15,16).

Hawkins have been reported that, with the application of FNAB in thyroid diseases surgical procedures ratio fell from 61% to 14% and preoperative diagnosis of thyroid carcinoma raised from 8.3% to 37.3%. These results are very important in terms of benefits of clinical application of FNAB (17).

'Follicular neoplasm' expression includes follicular development of groups of benign and malignant lesions originated from thyroid follicular epithelium. Despite the low rate of malignancy of these nodules, differential diagnosis should be made. In follicular, hurthle / oncocytic cell lesions, it is difficult to distinguish benign neoplasms from cancer with FNAB. Malignancy decision is made by the evaluation of capsular and / or vascular invasion in the post-operative histopathological examination. Such neoplasms constitutes a major portion of cases which can not be judged to be malignant for certain and put in a doubtful category and had surgery (7,9,18).

In the literature, postoperative rate of malignancy in patients with follicular neoplasm after cytological evaluation is noted as 20%-30%. In our study we found postoperative cancer rate as 20.4%. According to our results, it is noteworthy that in cases whose FNAB results were reported as hurthle cell neoplasms or oncocytic change, postoperative pathology did not report cancer. As with nodular thyroid disease, thyroid cancer is 3-4 times more common in women than men (20). In our study, among patients with postoperative cancer 16 of them were female, and 5 were male (F / M = 3.2 / 1).

In a study by Tyler and his colleagues it has been determined that, cytology results of follicular / Hurthle cell neoplasm increases malignancy risk by 40% in patients over 50 years old compared to patients under 50 years old (21). In our study, the age of patients ranged from 26 to 78. Although we observed an increased risk of malignancy with age, no significant correlation was found between age and gender and malignancy. Likewise, no statistically significant difference was observed when patients who got diagnosed with cancer postoperatively were evaluated according to goiter history, goiter type (solitary nodule / multinodular) and smoking history.

It is specified that, when the echogenicity of the nodule is hypoechoic according to the normal thyroid parenchyma echogenicity, malignancy probability raises compared to iso-or hyperechoic nodules (22,23,24). In our study, consistent with the literature, hypoechogenicity has been found to be statistically related with malignancy. In our study, hypoechoic monitoring of the nodule has been found as an independent predictive

Tablo 4. Comparison of patients' characteristics, results from FNAB (Follicular Neoplasm- Hurthle/Oncocytic cell Neoplasms) and postoperative malignancy results			
	Follicular Neoplasm (n=71)	Hurthle / Oncocytic cell Neoplasms (n=32)	p
Gender (male)	15 (21.1%)	7 (21.9%)	0.932
Type of goiter (MNG)	49 (69%)	21 (65.6%)	0.733
Smoking history	12 (16.9%)	5 (15.6%)	0.872
Ultrasonic Echogenicity* Hypoechoic Hyperechoic İsoechoic Mixed	16 (22.5%) 5 (7%) 18 (25.4%) 32 (45.1%)	8 (25%) 0 7 (21.9%) 17 (53.1%)	0.784 0.321 0.703 0.449
Ultrasonic Calcification* None Micro Peripheral Macro	54 (76.1%) 8 (11.3%) 2 (2.8%) 7 (9.9%)	21 (65.6%) 5 (15.6%) 0 6 (18.8%)	0.271 0.536 1.000 0.217
Scintigraphy* None Hypo İso Hyper	28 (39.4%) 29 (40.8%) 4 (5.6%) 10 (14.1%)	14 (43.8%) 12 (37.5%) 1 (3.1%) 5 (15.6%)	0.680 0.748 1.000 1.000
Post operative Malignancy	14 (19.7%)	7 (21.9%)	0.801
*Expected values were below 5 in more than 25% of the cells. Hence the tables were transformed to a 2x2 format and the comparison was made by using the chi-square test with the related category and the others. As such, a p-value is provided for each category level. Findings are given as "n (%)".			

factor for malignancy (OR: 6.064, 95% Confidence Interval: 1.878-19.584, p=0.003). In our study, nodules were seen in hypoechoic character in 53.3% of patients with papillary thyroid cancer and 50% of patients with follicular cancer. Overall malignancy rate for nodules which were evaluated as hypoechoic was 45.8%. No cancer was found in hyperechoic nodules.

In the literature, the presence of microcalcifications in nodules has been reported as the highest positive predictive value to detect malignancy (25,26,27). Among the sonographic criteria, it has the highest specificity (93%) but a low sensitivity (36%) (28). The risk of malignancy was found to be 2 to 3 times higher in solid nodules containing microcalcifications than nodules without microcalcifications (22,29,30). In our study, microcalcifications was observed in 20% of papillary thyroid cancer patients, yet no microcalcifications was detected in patients with follicular cancer. However, the presence of microcalcifications in nodules was not found to be significant in terms of malignancy.

In different surveys, carcinoma was reported in about 10%-25% of the nodules which were found to be hypoactive in scintigraphy (22,31). That rate reaches up to 35% in some other studies (32,33). Greenspan et al. gave the rate as 15%-20% (34). In our study, the rate of malignancy in hypoactive nodules was found to be 21.9%, but no significant difference was observed between scintigraphic features of the nodules and malignancy.

Hamming et al. found the rate of malignancy as 27% in their study in cases with MNG who has solitary nodules and a dominant nodule with a diameter of at least 40 mm long, and solid components over 75% (35). Also, Bildik et al. have found the malignancy rate as 14.9%, in nodules 3 cm and above; as 3.2% in nodules smaller than 3 cm. This indicates that the malignancy rate of 3 cm and above nodules are about 4.6 times more than that of the nodules smaller than 3 cm (36). Unlike Hamming et al. and Bildik et al, however, no significant association was found between the nodule size and the malignancy in our study (35,36). Bayrak et al. have concluded that in patients with MNG, no difference was detected between the FNAB results of dominant nodule and the nonspecific nodules (37). Similarly, no significant correlation was found between the nodule size and the malignancy in the study done by Sengoz et al (38).

According to Papini et al, parameters like the existence of single or multiple nodules in the thyroid gland, dominant nodules, or nodules that are larger than 1 centimeter, are not directly related to malignancy (29). In their study published in 2004, Ceresini et al. found no statistically significant correlation between malignancy and the nodules' diameter (39). There was no correlation between nodule size and malignancy in Berl et al.'s study either (15). Similar to the results from all these studies, our study found no statistically significant correlation between nodule size and malignancy.

In our study, preoperative FNAB results and postoperative histopathologic findings of these nodules have been compared to each other. A large portion of patients were MNG, because of this, malignancy result may have been obtained from another nodule. As a result, 1/5 of cases reported follicular neoplasms, oncocytic change and Hurthle cell neoplasm based on FNAB results, have revealed malignancy and these nodules are independent risk factors in predicting the hypoechoic appearance of malignancy in thyroid US. Especially the ultrasonographic evaluations of the cases with follicular neoplasm and Hurthle cell neoplasm based on FNAB results should be reevaluated and it should be kept in mind that those which have hypoechoic character could be malignant. Moreover, in such patients, the size of nodules are not significant in the prediction of malignancy, it should be known that small nodules can have malignant characteristics as well.

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